We have added the requested text.

v. ***If space permits, add the storage recommendation statement.***

Space does not permit.

2. Carton

a. ***Revise the "usual Dosage" statement to read as instructed in comment 1(e)(iv).***

We have added the requested text.

b. ***Please refer to comments 1(a, c, d and e) under Container (pouch).***

a. We are unable to comply with this request at this time due to the intricacies involved with our distributors' container labels of contrasting colors and/or boxing.

b. We have found that this is unnecessary due to the fact that the name is already arranged as you have requested.

c. We have complied with your request.

d. We have added the requested text.

e.

i. We have added the requested text.

ii. We are unable to comply with this request due to limited space.

iii. We have added the requested text.

iv. We have added the requested text.

v. This statement is already present.

3. Professional Package Insert

a. ***General Comment:***

Use consistent format when referring to section headings in the text of the insert (i.e., see CLINICAL PHARMACOLOGY).

We have added the requested emphasis for consistency.

b. ***DESCRIPTION:***

i. ***Add the statement, "The inactive ingredients are: polyester film, silicone and acrylic adhesive with a cross-linking agent.***

This is an inaccurate description of our product. We have added a more appropriate statement to describe the inactive ingredients in our formulation.

ii. ***Revise the last paragraph to read as follows:***

Each system contains nitroglycerin in acrylic based polymer adhesive with a cross-linking agent to provide a continuous source of active ingredient. The nitroglycerin transdermal system comprises three layers; 1) the outer backing which is composed of a polyester film and is printed with the name of the drug and strength; 2) nitroglycerin in acrylic-based polymer adhesive; 3) a protective peel strip which covers the second layer and must be removed prior to use. Each system is sealed in a paper polyethylene-foil pouch.

This statement is inaccurate. We have modified the text as you have requested with an accurate description of our product.

iii. ***Diagram***

We encourage you to revise the description of your layers to read as follows:

OUTER BACKING
(impermeable)
SECOND LAYER
(nitroglycerin in adhesive)
PROTECTIVE PEEL STRIP
(release liner)

We have modified our diagram to reflect the above.

c. Information for the Patient:

i. ***When describing the backing/protective liner, use a phrase such as "...it has translucent white backing with a peelable liner divided into two strips.." instead of "prescored".***

We have added an accurate statement as requested.

ii. ***We encourage you to add the "Usual Dosage: Each 24 hour.." statement, following the text under "Important".***

We have added the above.

d. ***HOW SUPPLIED***

Add the text, "clear white backing" to the physical description of system.

We have added the requested text.

4. Patient Package Insert

Please refer to our comment 3 (c) under Information for the patient.

We have added the requested text.

The above information should completely support our size changes for the three strengths of our nitroglycerin Transdermal System. Additionally, I believe we have adequately answered all labeling concerns.

This Major Amendment consists of one volume for ANDAs 89-884 and 89-885 and sixteen volumes for ANDA 89-886. Hercon is filing an archival copy and a technical review copy, which contains all of the information in the archival copy. The archival and technical review copies are separated into a CMC section and Bioequivalence section to facilitate concurrent review of the application. This also certifies that a true copy of the CMC section of this submission has been filed with the Philadelphia District Office and includes a copy of FDA Form 356h and a certification that the contents are a true copy of that filed with the Office of Generic Drugs as required by 21 CFR 314.5 (k)(3).

Please call me at (717) 764-1191 if you need further information.

Sincerely,

Robert M. Pilson, R.Ph., J.D.
Director of Regulatory Affairs

cc: Timothy W. Ames (cover letter only)
Project Manager
CDER, OGD, DLPS
Metro Park North II
HFD 617
7500 Standish Place
Rockville, Maryland 20855-2773

Jerry Phillips (cover letter only)
Director
Division of Labeling and Program Support
CDER, OGD, DLPS
Metro Park North II
HFD 613
7500 Standish Place
Room 200N
Rockville, Maryland 20855-2773

Diane Kolaitis
District Director
Philadelphia District Office
FDA-A
U.S. Customhouse
Second & Chestnut Street
Room 900
Philadelphia, Pennsylvania 19106

HERCON LABORATORIES
CORPORATION

P.O. Box 786, York, PA 17405 • (717) 764-1191 • Fax: (717) 764-5395

[redacted]

NC

7.1

June 5, 1997

Mr. Timothy W. Ames
Sr. Supervisor, Regulatory Affairs
CDER/OGD/DLPS
Food and Drug Administration, HFD617
Metro Park North 2, Room 113
7500 Standish Place
Rockville, MD 20855

Dear Mr. Ames:

FACSIMILE AMENDMENT

Re: ANDA89-884
ANDA89-885
[redacted]

I am writing in response to your facsimile of May 7, 1997 (copy enclosed), regarding the above-captioned ANDA's. I will answer your comments in the order presented.

- **Please update your patent certification.**

  Our original patent certification dated April 16, 1993, is enclosed as Attachment 1. Based on 21 CFR 314.94(a)(12)(vi) pertaining to "Late Submission of Patent Information", we are not required to re-certify against the Ciba patents that first appeared in the Orange Book in the January '96 to December '96 Cumulative Supplement (copy of page enclosed as Attachment 2). The approval of Ciba's Transderm Nitro® first appeared in the Orange Book in the January '96 to February '96 Cumulative Supplement (copy of pages enclosed as Attachment 3). The patents appeared in the Orange Book a full ten months after the Ciba Transderm Nitro® approval appeared in the Orange Book.

- LABELING ISSUES

  1. **Delete from your labels and labeling.**

     Twelve (12) draft copies of the appropriately revised Patient Package Insert, Professional Package Insert, Pouch Labeling and Shelf Carton are enclosed (see Attachments 5, 6, 7 and 8).

2. Patient Package Insert Labeling

Revise your patient package insert labeling to be in accord with the enclosed approved patient package insert labeling of Transderm-Nitro (nitroglycerin) Transdermal System [Approved 5/19/94 and revised 7/93]. Please note, minor modifications may be required due to drug product differences.

Twelve (12) draft copies of the revised Patient Package Insert Labeling enclosed as Attachment 5.

3. Professional Package Insert Labeling

a. **DESCRIPTION: List the imprinting ink which is used on the patch, as requested in our letter dated March 29, 1996.**

According to the supplier of the imprinting ink, the dried printed ink contains only (Letter from enclosed as Attachment 4.)

b. **HOW SUPPLIED: Revise "and the strength in mg/hr" to read "and the release rate in mg/hr".**

Twelve (12) draft copies of Professional Package Insert enclosed as Attachment 6.

c. **See comment under Patient Package Insert and revise the information reprinted at the end of your insert accordingly. In addition, we note you have revised the fifth pictorial patient instruction, which differs from your last submitted insert labeling, as well as your patient package insert labeling. The intended patient instruction to be conveyed from this picture is unclear. Please revise and/or comment.**

Twelve (12) draft copies of Professional Package Insert enclosed as Attachment 6.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Patient Package Insert
Completely revised to match Transderm-Nitro (nitroglycerin) [approved 5/19/94].

Pouch Labeling
Removed designation
Relocated 1 system

Shelf Carton
Removed designation
Relocated 30 systems

Side-By-Side Comparison
Professional Package Insert with Professional Package Insert submitted October 10, 1996.

May, 1997
Removed designation
Description (second paragraph, seventh line) - "deliver approximately"
How Supplied - "and the release rate in mg/hr"

Reverse Side
Revised in accord with Transderm-Nitro (nitroglycerin) Transdermal System [approved 5/19/94]. Also, fifth pictorial has been replaced with the appropriate pictorial.

We believe that we have complied with the requests in your facsimile. We are submitting draft labeling in a side by side comparison as requested.

Sincerely,

Robert M. Pilson
Director
Regulatory Affairs

RMP/leb
attachments

cc: Peter Rickman (Fax: 301-594-0181)
John Grace (Fax: 301-443-3847)
Jerry Phillips (Fax: 301-443-3847)

HERCON LABORATORIES
CORPORATION

P.O. Box 786, York, PA 17405 • (717) 764-1191 • Fax: (717) 764-5395

November 27, 1996

NEW CORRESP

NOV 6 7 199.

NC

Mr. Douglas L. Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration, HFD-600
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

via Certified Mail
Return Receipt Requested

Re: **Nitroglycerin Transdermal System:** **ANDA #89-884; 0.2 mg/hr**
ANDA #89-885; 0.4 mg/hr
ANDA [redacted] 0.6 mg/hr

Dear Mr. Sporn:

Thank you for your letter of November 19, 1996, following up on our earlier letter of October 16, 1996. We appreciate your reviewing the history of the above-referenced ANDAs. In our letter to the FDA Chief Mediator and Ombudsman, we tried to focus on why we believe the review period experienced by these applications has been quite lengthy. In doing this, we focused on information about the review periods while the applications were with the FDA (not while they were awaiting our action), and on information about the periods that took the most time (that is, the bioequivalence reviews rather than the chemistry reviews). We honestly do not believe that we "mischaracterized" the situation, as you suggested. Rather, we have simply tried to express our concern that the reviews really have taken an awfully long time.

As reflected in our letter to the Ombudsman, it appears that, in part, the length of the review period may have resulted from issues raised as a result of our following the "Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs," 58 FR 39406 (July 11, 1993). We have worked hard to help the Agency address these issues, and we continue to believe that these can be resolved promptly in favor of our ANDAs.

We believe that a prompt review of our applications is appropriate at this time, both for reasons of fairness, in light of the history of these applications, and for reasons of science, so that the "gender differences" issues can be addressed before they become a problem for other applications. These issues arose as a consequence of our strict compliance with this FDA guideline. Surely we should not be penalized for being the first company to so comply in a bioequivalence study.

Therefore, we respectfully request that our applications (including our amendment dated October 10, 1996) be reviewed on a priority basis. Please be assured that we wish to work in full cooperation with you and are prepared to assist in any way should you have any further questions about our applications.

Thank you for your consideration of this request.

Sincerely,

Robert M Pilson

Robert M. Pilson, R.Ph., J.D.
Director
Regulatory Affairs

RMP:bjf

cc: Mark Anderson (HFD-617), DLPS/OGD/CDER/FDA
Thomas J. Atkins, Ph.D., Hercon Laboratories Corporation
James Morrison (HFD-100), Ombudsman for CDER, FDA
Amanda Bryce Norton (HF-7), Chief Medicator and Ombudsman, FDA
Bruce Schloss, Health Chem Corporation
Roger Williams, M.D., (HFD-003), Director, OPS/CDER/FDA

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November 22, 1996

MINOR AMENDMENT TO MAJOR AMENDMENT DATED OCTOBER 10, 1996

Rabindra N. Patnaik, Ph.D.
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

via Federal Express

Re: Nitroglycerin Transdermal System:

ANDA #89-884	**0.2 mg/hr; 6.75 cm²**
ANDA #89-885	**0.4 mg/hr; 13.5 cm²**
ANDA #89-886	**0.6 mg/hr; 20.25 cm²**

RETEST OF SUBJECT 121 IN A REPLICATE DESIGN FROM STUDY PROTOCOL #567794 ORIGINALLY PERFORMED APRIL, 1994

Dear Dr. Patnaik:

Based on a suggestion made at our meeting with representatives of the Bioequivalence Division on August 23, 1996, Hercon performed a retest of Subject #121 from the above captioned study. In the original study, Subject #121 behaved as a statistical and metabolic outlier. The retest of Subject #121 in a replicate crossover design shows that he attained blood levels more in line with the blood levels achieved by the remaining male subjects in the original study. The Supplemental Report prepared by('s attached herein and identified as *Attachment 1.*

Based on the data obtained in the retest, we feel that Subject #121 does not replicate himself with either the reference or the test drug and was clearly an outlier in the original study. Therefore, we feel his data should be excluded from the original study. Analysis of the data from the original study then would show that the test drug is bioequivalent to the reference drug using conventional statistical methods from the Bioequivalence Guidance dated July 1992 .[1]

---

[1] The FDA has stated that "outliers cannot be dropped from the analysis of the data solely on the basis of a statistical test. Sponsors who have identified one or more outliers should provide scientific evidence or explanations to justify the exclusion of the subject(s) data from statistical analysis." "Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design" (July 1, 1992).

We hope this information answers all outstanding questions. Please contact me at (717) 764-1191 if you need further information.

Very truly yours,

Robert M. Pilson, R.Ph.., J.D.
Director
Regulatory Affairs

RMP:bjf

Enclosure

cc: (Cover letters only): Mark D. Anderson, CDER, OGD, DLPS
Douglas Sporn, Director, OGD, FDA
J. Morrison, Ombudsman, FDA
T. Atkins, Ph.D., Vice President, Hercon Laboratories Corporation

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October 10, 1996

MAJOR AMENDMENT
ND

RECEIVED
OCT 15 1996
GENERIC DRUGS
Via Federal Express

Rabindra N. Patnaik, Ph.D.
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: **Nitroglycerin Transdermal System:**

ANDA 89-884	0.2 mg/hr; 6.75 cm^2
ANDA 89-885	0.4 mg/hr; 13.5 cm^2
ANDA 89-886	0.6 mg/hr; 20.25 cm^2

Dear Dr. Patnaik:

I am writing in reference to your letter dated November 30, 1995 (copy enclosed and identified as **Attachment #1**). In regard to the above captioned ANDA's, we will address each comment in the order in which it was presented.

Item 1: *The bioequivalence study conducted to support approval of these application has failed to satisfy the appropriate bioequivalence criterion:*

a. For nitroglycerin (TNG) the 90% Ln-transformed confidence intervals for $LnAUC_{0-inf}$ are outside the 80-125% limit.

b. For 1,3-dinitroglycerin of test product, the 90% Ln-transformed confidence intervals for $LnAUC_{0-7}$ (77; 88), $LnAUC_{0-14}$ and $LnAUC_{0-24}$ (78; 89) are outside the acceptable range of 80-125% .

(a) The issue of ln-transformed confidence intervals being outside the 80-125% limit was addressed in our February 7, 1996, submission (copy of the four-page cover letter is attached and identified as **Attachment #2**) on page 3, paragraph 2 of the cover letter and the statistical re-analysis which is included in this set of correspondence.

(b) This is discussed in the outlier analysis on page 38 of this submission.

Item 2: *The dosing of Group 2 in Period 1 was started (4/30/94) a week after the dosing of Group 1 in Period 2 (4/23/94)...*

The reason for the separation was not to make two separate groups but that we did not have the whole study recruited as of 4/23/94. The model suggested in #2 is the reduced model that appears in Appendix D-1 which also includes a gender term.

Item 3: *Please clarify why the in vivo bioequivalence study was conducted in 36 subjects, but reported "40 subjects" in all headings of Tables and Figures in the study report.*

Item 3 requests clarification as to why the table headings reflected "40 subjects" while the statistical analysis was conducted in 36 subjects. The answer to this question is stated in numerous places in the submission. The headings reflected 40 subjects based on the title of the protocol – "Bioequivalence Evaluation of Two Nitroglycerin Patches in 40 Healthy Volunteers." Per the protocol, 40 subjects were entered into the study and were properly included in the safety evaluation. Four subjects voluntarily dropped from the study, leaving 36 completers for statistical evaluation. It is inappropriate to change the title of the study after it was completed, just because some of the enrolled subjects dropped out. There was certainly no intent to mislead the Agency.

Item 4: *The residual content data for nitroglycerin in the patches used were not included in the submission.*

This is a redundant deficiency. Hercon was notified in our previous letter dated August 18, 1994, that this data was required.

The residual content data for nitroglycerin in the patches used were included in our submission dated December 8, 1994, pages 1435 - 1447, copies of which are provided again herein and are identified as **Attachment #3.**

Items 5 & 6:

Item 5. *The dissolution (drug release) testing conducted by Hercon Laboratories on its Nitroglycerin Transdermal System Face Adhesive Patch, 0.4 mg/hr, Lot #M0504NG/556 comparing it to Transderm-Nitro®, 0.4 mg/hr, Lot #C5340, manufactured by Ciba-Geigy is incomplete. The first time point in the release rate data submitted to the Agency is a 30-minute time point, however, the proposed drug release specifications contain 15-minute time point. The appropriate specifications should be established for the release rate of the test product from the data obtained in the drug release study.*

Item 6. *The drug release data were derived from 6 dosage units of 0.2 mg/hr and 0.6 mg/hr patches. Please be advised that in vitro*

dissolution (drug release) testing should be conducted on 12 individual units of the test and reference products and the summary report should include the raw, mean, range and coefficient of variation data.

This is a redundant deficiency, Hercon was notified in our previous letter dated August 18, 1994, that this data was required.

Dissolution (drug release) testing and drug release data are included herein and marked as **Section VI.D.** The dissolution testing including the 15-minute time point and the 12 units was performed in December 1995. Our reference drug Transderm-Nitro®, Lot #C5340, expired in September 1995 and was not appropriate for use in the dissolution testing. We apologize for not using the biostudy lot in the dissolution testing. This was primarily because of some significant personnel changes made at the time. It is our hope that the results contained herein are representative of the reference product used in the biostudy.

We hope this answers all of the concerns listed in your letter of November 30. We feel that the information presented in this submission will prove our product to be bioequivalent to Ciba's product, Transderm-Nitro®. Please call me if you have any questions regarding these issues.

Very truly yours,

Robert M. Pilson, R.Ph., J.D.
Director
Regulatory Affairs

:bjf

Attachments

Desk Copy: (cover letter only)
Mark D. Anderson, CDER, OGD, DLPS
HFD-617
Metro Park North II
7500 Standish Place, Room 113
Rockville, MD 20855

HERCON LABORATORIES
CORPORATION

P.O. Box 786, York, PA 17405 • (717) 764-1191 • Fax: (717) 764-5395

October 10, 1996

MAJOR AMENDMENT

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Document Control Room
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Label
Ac

via Federal Express

Re:	ANDA 89-884	Nitroglycerin Transdermal System	0.2 mg/hr
	ANDA 89-885	Nitroglycerin Transdermal System	0.4 mg/hr
	ANDA 89-886	**Nitroglycerin Transdermal System**	**0.6 mg/hr**

Dear Mr. Sporn:

I am writing to you in response to your letter of March 29, 1996 (copy enclosed).

Regarding the deficiencies noted in the above referenced letter, the following actions have been taken:

A. Chemistry Deficiencies

"The individual unit specifications for in-process control of the bulk lamination (%) are not consistent with your final drug product specifications or with USP specifications for transdermal patches. Please revise your in-process specifications to be consistent with your final in-process specifications to be consistent with your final drug product specifications and compendial requirements."

We have revised our Product Testing Document #1021NG to be identical to the USP specification. These revisions are reflected in the enclosed document marked as **Attachment #1.**

B. Labeling Deficiencies

"Professional Package Insert Labeling:

1. DESCRIPTION
   a. Revise the last sentence of the third paragraph to read: ...delivered approximately 7% of ..."
   b. List the imprinting ink which is used on the patch.

Mr. Adolph Vezza, Labeling Reviewer, Office of Generic Drugs, stated in a telephone coversation on May 20, 1996 that we do not have to list the imprinting ink. Mr. Vezza authorized us to use his name in our response.

2. *PRECAUTIONS*

   a. *Carcinogenesis, Mutagenesis, Imparment of Fertility*
      i. *Delete the from the subsection title.*
      ii. *Delete the penultimate sentence of the second paragraph (Incidences...females).*
   b. *Revise the subsection title as follows: Pregnancy: Pregnancy Category C:*

We have made all of the changes requested in your letter; in addition, we have made appropriate punctuation and grammatical changes. Four mounted copies of the Professional Package Inserts are enclosed and marked **Attachment #2.** Eight loose copies are enclosed in the envelope included with this submission.

We hope that this letter answers your concerns. We look forward to an early approval to our application.

Very truly yours,

Robert M. Pilson, R.Ph., J.D.
Director
Regulatory Affairs

:bjf

Enclosures: March 29, 1996 deficiency letter from FDA
FDA Form 356H
Attachment #1
Attachment #2

cc: Desk Copy: Frank O. Holcombe, Jr., Ph.D.
Director, Division of Chemistry II, HFD-621, Room 204
Field Copy: Philadelphia District Office

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NAI
To Bio for response / FYI
7/17/96

NEW CORRESP [redacted]

July 15, 1996

RECEIVED
JUL 16 1996
GENERIC DRUGS

Keith K. Chan, Ph.D., Director
Division of Bioequivalence (HFD-630)
Office of Generic Drugs
Center for Drug Evaluation and Research
Department of Health & Human Services
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room E-130
Rockville, Maryland 20855

via Federal Express

Re: ANDA No. 89-884
ANDA No. 89-885
ANDA No. 89-886

Dear Dr. Chan:

Hercon Laboratories respectfully requests a meeting with representatives of the Center for Drug Evaluation and Research to discuss issues relevant to the bioequivalence status of Hercon's pending ANDA's for transdermal nitroglycerin: ANDA 89-884, 89-885, and 89-886. Hercon received a "not approvable" letter dated November 30, 1995 concerning our bioequivalence study submitted on December 8, 1994. Additionally, we received a letter dated June 25, 1996 in response to our statistical re-analysis submitted February 7, 1996.

Our request for a meeting has three main objectives:

1) To provide responses to all of the bioequivalence deficiencies raised in the November 30, 1995 letter (enclosed) as well as address the issues of the June 25, 1996 letter (enclosed). These responses will include utilization of the ANOVA models suggested in both letters to reach a consensus on how best to respond to these deficiencies.

2) To provide pharmacokinetic and statistical justification utilizing additional statistical analysis in assessing bioequivalence of nitroglycerin transdermal systems.

3) To introduce our new Vice President of Research and Development, Dr. Tom Atkins, and our new Director of Regulatory Affairs, Bob Pilson.

7/23/96

Because of the pharmacokinetic and statistical issues inherent with the analysis of the bioequivalence of a transdermal nitroglycerin product, we believe a meeting is necessary to respond to the Agency's concerns. Additionally, we would like to provide clarification of our position and openly discuss the issues.

To facilitate the discussion and to make the meeting as productive as possible, Hercon will be represented by:

Thomas J. Atkins, Ph.D.	Hercon Laboratories Vice President, Research and Development
Robert M. Pilson	Hercon Laboratories Director, Regulatory Affairs
Bernard E. Cabana, Ph.D.	New Drug Services Clinical Research Consultant
Michael Adams, PharmD.	New Drug Services Clinical Research Consultant
John Conlon, Ph.D.	Reliable Research Statistical Consultant

Our proposed agenda includes several items, but we are open to any issues that the Agency may wish to add:

I.	Introduction	Robert M. Pilson
II.	Point by Point Response to deficiencies raised in letters of November 30, 1995 and June 25, 1996	Bernard Cabana, Ph.D. John Conlon, Ph.D. Robert M. Pilson
III.	Pharmacokinetic and Statistical Analysis	Bernard Cabana, Ph.D. John Conlon, Ph.D.
IV.	Discussion	
V.	Timeframe for Response	Robert M. Pilson

In this regard, we respectfully request that the FDA representatives at the meeting include individuals experienced in the pharmacokinetics of nitroglycerin analysis. We propose that the meeting be attended by the following Agency personnel in addition to any others the Agency deems appropriate:

Roger Williams, M.D.
Charles Ganley, Ph.D.
Keith Chan, Ph.D.
Lawrence J. Lesko, Ph.D.
Donald Schuirman

Thank you for the opportunity to request this meeting. Please call me at (717) 764-1191 if there are any questions regarding our proposal.

Very truly yours,

Robert M. Pilson

Robert M. Pilson
Director
Regulatory Affairs

RMP:bjf

Enclosures

cc: M. Adams, PharmD., New Drug Services, Inc.
T. Atkins, Ph.D., Vice President R&D, Hercon Laboratories Corporation
S. Barnhart, Hercon Laboratories Corporation
D. Buerger, Ph.D., Hercon Laboratories Corporation
B. Cabana, Ph.D.; NDS International Inc.
J. Conlon, Ph.D., Reliable Research
D. Kauffman, Vice President Manufacturing, Hercon Laboratories Corporation

Desk Copy: Jason Gross, Pharm.D., FDA, HFD-612, Room 113

HERCON LABORATORIES
CORPORATION

P.O. Box 786, York, PA 17405 • (717) 764-1191 • Fax: (717) 764-5395

MAJOR AMENDMENT

August 7, 1995

AMENDMENT
M/AC
PPL

review due
3.1.96
a Vgp

Florence S. Fang, Acting Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

via Fedex
airbill # 5672174443

RE: Nitroglycerin Transdermal System:
ANDA 89-884; 0.2 mg/hr; 6.75 cm²
ANDA 89-885; 0.4 mg/hr; 13.5 cm²
ANDA 89-886; 0.6 mg/hr; 20.25 cm²

Dear Ms. Fang:

Reference is made to your June 14, 1995 not approvable letter concerning the Abbreviated New Drug Applications identified above. To address the deficiencies cited therein, Hercon Laboratories Corporation is providing this Amendment to our applications. Your letter identified this response as being considered a Major Amendment.

NOTE that these Amendments, and the underlying applications, are virtually identical to those relating to another set of ANDAs which we have submitted concurrently for slightly different die-cut patch sizes of the products (and for which a corresponding not approvable letter was issued by the Agency, also on June 14, 1995). Similar to the previous review which led to the above-identified deficiency letter, we suggest that it would be most efficient for our responses concerning all six submissions to be reviewed together by a single chemist or a team working together. For convenience, listed below are the supplement numbers of the other three related submissions:

ANDA
ANDA
ANDA

The numbering system of the responses set forth below corresponds with that of the deficiencies cited in your June 14, 1995 letter. All of the requisite documentation to respond to each individual deficiency is generally grouped together under a single attachment Tab as described in the written response for that deficiency.

RECEIVED
AUG 0 8 1995
GENERIC DRUGS

8-22-95

Redacted 4

pages of trade

secret and/or

confidential

commercial

information

Chem. Deficiencies

B. Labeling Deficiencies

General Comments:

a. The terminal zero following the decimal point has been deleted when expressing the system size.

b. We have devised a simple, yet effective mechanism for differentiating between the products covered by these applications and those covered by the Supplements to ANDAs We have assigned each set of products a distinctive two-letter code which is visibly different at a glance of the labeling. Additionally, the product name and strength for one set of products is printed in italic type, while the other is not. We believe that any qualified pharmacist employing reasonable care will now be able to distinguish easily between these products and provide the proper product for substitution.

c. The revised insert described below contains a complete reprint of the patient informational brochure at the end.

Note that as requested, final printed labeling has been prepared. The printed labeling is presented in *Attachment 11*. A total of 12 final printed copies are provided, as follows: the archival copy of this submission contains three mounted copies and eight loose copies (in an envelope) of each labeling piece; the review copy contains one mounted copy. Note that we have attached transparencies showing die cut lines to the mounted carton labeling, so that the reviewer can easily discern what an actual box will look like. The labeling has been revised to address all of the cited deficiencies. Specific responses to each deficiency are provided below, with the numbering corresponding to that of your June 14, 1995 letter.

Container (Pouch):

1. We believe the revised labeling adequately differentiates among the strengths. Each strength is clearly and very prominently presented. In addition, note that the pouch sizes are visibly different for the three strengths, so there is no potential for mix-up or confusion. Because Hercon often private-labels its products for a number of distributors, differentiation by color is impractical, since most distributors have their own unique trade dress color schemes.

2. Front Panel:

a. The size of the system has been prominently displayed in parentheses adjacent to the strength, as requested.

b. The "Each ____ cm^2 contains..." statement has been revised as requested.

c. As requested, the referenced statement has been changed to: "APPROXIMATE RATED RELEASE *IN VIVO* ____ mg/hr".

Carton (30's):

1. Front Panel: The changes as noted under "Container (Pouch)" have also been made to the carton.

2. Left Side Panel: The Usual Dosage statement has been revised as requested.

3. Right Side Panel:

a. The "Do not refrigerate" storage statement was added to the carton.

b. Pictorials have been added to the carton to assist in proper product application by the patient.

Patient Package Insert:

1. The revised patient package insert is complete in that it now contains the pictorials.

2, 3, and 4. The requested changes have been made to the patient insert. We note that the changes requested to the patient insert for our pending supplemental applications for other nitroglycerin patch sizes (ANDAs) would make that patient insert identical to the one for the product sizes covered by this application. Since the patient insert is not patch size-specific we see no need to prepare and internally control two separate identical patient inserts. Accordingly, the patient insert for all six applications is identical. This eliminates the difficulties of control and unnecessary redundancy.

Insert (professional):

1. "Prescribing Information" has been deleted from the top of the insert.

2. DESCRIPTION:

a. During our insert revision process, your comment was misunderstood and the stated text was accidentally inserted into paragraph 2, not 3. We hereby commit to correct this typographical error in paragraph 2 and add "approximately" to the

delivery statement in paragraph 3, at the first printing. The insert will be corrected prior to shipping any product after approval. Any product to be marketed will contain only the corrected insert as described. Per 21 CFR §314.70(d)(3) an editorial change of this type may be reported in the next Annual Report for the product, which we also commit to do.

b. We apologize sincerely for this error. When this application was submitted, to assure that our proposed labeling conformed exactly to the current approved labeling for our existing nitroglycerin transdermal products (ANDAs), we prepared draft labeling by photocopying our approved insert, making changes that were appropriate for the differences between the products. Unfortunately, this statement referencing the patch composition was somehow overlooked. The revised insert corrects this error.

3. WARNINGS: The requested change has been made to paragraph 2.

4. PRECAUTIONS:
   a. The requested change was made in paragraph 5.

   b. The reference has been added to patient information at the end of the insert.

   c. The two paragraphs have been combined into one.

   d. The requested change to "Pediatric Use" was made.

5. ADVERSE REACTIONS:
   a. The position of the second and third paragraphs was switched.

   b. The paragraph referring to "methemoglobinemia" was revised as stated; however, we must note that the previous wording had been specifically requested by the Agency a few years ago in a letter concerning our ANDAs . The presently-requested wording is the way it used to be.

   c. The "application site irritation" paragraph was relocated.

6. HOW SUPPLIED: A description of the patches and their direct printing has been added to this section, as seen in the innovator's insert.

Also as requested at the conclusion of your letter, we have noted the points raised concerning expiration dating, and we acknowledge the following:

1. The drug product expiry dating will be calculated based on the date of manufacture of the original laminate, not on the date of manufacture of the slit laminate or die-cut patches.

2. Based on our commitment as stated above, the original or slit laminate may be stored for up to six months as proposed in this application.

In addition, please be advised that Hercon received a pre-approval inspection concerning this product by representatives of the FDA Philadelphia District during June 1995. A Form 483 was issued containing two observations, corrective actions for both of which were underway during the inspection. Hercon issued a formal response to the District completely addressing the citations, and we were informed orally that based on our responses the District planned on issuing to the Center a notice of concurrence with approval.

So that these ANDAs are complete with respect to all of the controls employed, we are providing as part of this Amendment (*Attachment 12*) a complete copy of our response to the Form 483, including all attachments thereto. Our response put into place certain controls requested by the Investigator, and provided several Research Reports justifying the controls or providing additional data concerning some of our analytical methods. By submitting this information, we hereby commit in the application to employ these controls. The principal information provided is as follows:

- Updated controls for the drug substance (nitroglycerin-containing polymer adhesive) which include an Identification test by infrared spectroscopy to assure the consistency of the polymer blend from batch to batch.

- Updated controls for the processing aid, silicone treated release liner, to include testing for silicone coating weight and "release" strength, to better assure that the material coats properly during the manufacturing process.

- Additional data identifying every peak in the chromatogram generated by the "Related Compounds" test for the raw material, which definitively show that there are no interferences with the analyte peaks. Note that because the chromatographic systems for determination of related compounds are the same for both the final product and the raw material, the applicable peak identities correspond for both methods. Sample representative chromatograms are attached to the test methods as provided in *Attachment 10.*

Note that following the inspection, we further updated the revised raw material specifications for the silicone treated release liner to provide more detailed references to the test methods. The updated specifications are provided as *Attachment 13*, and replace those from the Form 483 response in Attachment 12.

Please note: The Agency's companion Not Approvable letter concerning our supplements to ANDAs cited another deficiency concerning our Categorical Exclusion request for an environmental assessment, that was not cited in the letter relating to these applications (ANDAs 89-884, 89-885, and 89-886). So that these applications are complete and consistent with those supplements, we are providing as *Attachment 14* a revised Categorical Exclusion request which certifies compliance with all applicable environmental laws.

We note that although your letter states that we will be notified in a separate letter of any deficiencies in the bioequivalence portion of our application, we have not yet had any response from the Division of Bioequivalence, although the review is now pending nearly 9 months. We are dismayed by this long delay in receiving a response.

Hercon Laboratories trusts that the above responses will be sufficient to remove the cited deficiencies and allow approval of our application, particularly in light of our having already completed a satisfactory pre-approval inspection. We believe that these applications are very complete and well-documented. If because of the nature of the products there is any confusion, or if you have any questions or need any additional information, please do not hesitate to contact the undersigned at your convenience. Since transdermal products are relatively new and somewhat unique, we respectfully suggest this approach to avoid undue delay caused by a simple misunderstanding. In this way, a question about one of the documents or batch records can most likely be addressed easily over the phone. Thank you for your consideration.

We hereby certify that a complete copy of this amendment has been sent concurrently to Hercon's home FDA District Office (Philadelphia District).

Very truly yours,

Joseph J. Sobecki, R.A.C.
Senior Director
Regulatory Affairs
Hercon Laboratories Corporation

JJS:js
attachments

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MAJOR AMENDMENT

December 8, 1994

BIOAVAILABILITY

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

N/A C
AMENDMENT Draft Labeling

via Federal Express
airbill # 0855597352

RE: **ANDA 89-884**; Nitroglycerin Transdermal System, 0.2 mg/hr
ANDA 89-885; Nitroglycerin Transdermal System, 0.4 mg/hr
ANDA 89-886; Nitroglycerin Transdermal System, 0.6 mg/hr

Dear Sir or Madam:

Reference is made to Mr. Douglas Sporn's August 18, 1994 not approvable letter concerning the Abbreviated New Drug Applications identified above. To address the *in vivo* study deficiencies cited therein, Hercon has "re-sized" our product and conducted a new bioequivalence study, as detailed in this Amendment to our applications. The changes to the product, as described herein, relate solely to the die-cut unit size of the finished patches. The patches are cut from exactly the same laminate stock as previously described in this application.

The results of the previously-submitted bioequivalence study indicated that the drug delivery from the Hercon product was higher in that study than that of the reference product, Summit's (Ciba's) Transderm-Nitro®. Because the rate of release of nitroglycerin from transdermal systems is known to be linearly related to the surface area of the patch, Hercon attempted to determine what reduction in patch size would be needed to achieve confidence intervals within the guideline ranges for nitroglycerin and its principal metabolites. It was decided that a 10% reduction in patch size would achieve the desired results. Accordingly, the patch sizes for the 0.2, 0.4 and 0.6 mg/hr strengths were reduced from 7.5, 15.0, and 22.5 cm^2 to 6.75, 13.5, and 20.25 cm^2, respectively. The per-unit-area formulation and all of the other manufacturing and control characteristics remain exactly the same. The die-cut size of the patch is only determined at the final stages of manufacture; thus, almost all of the chemistry, manufacturing, and controls information previously reviewed by the Agency under these applications remains relevant.

This amendment contains all of the bioequivalence, chemistry, and labeling documentation changes necessary due to the change in patch size. In addition, actual test results and batch records for the "biobatch" and its components are included. Except for the documentation provided herein, the remainder of the information previously provided remains the same and is entirely relevant to the reduced-size product. This includes not only the component and container-closure controls, but also the basic manufacturing procedures.

9 1994

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Received
12-9-94

Due to the fairly significant amount of documentation included which reflects various sections of the ANDA, and to keep the related information together, **this submission has been organized in the same order as the ANDA.** Tabs have been included for the applicable sections of the ANDA for which revised or additional information is provided in this amendment. For simplicity, tabs for sections with no changes are not provided. Those sections are listed as "not applicable" in the Table of Contents. Please refer to the Table of Contents following this cover letter for a complete listing of the information provided in this amendment.

Although the new bioequivalence study stands on its own in addressing all of the relevant comments in your August 18, 1994 letter, we are providing below brief responses to the specific deficiencies cited therein.

1. BIOEQUIVALENCE STUDY

Deficiency 1 a:
"For nitroglycerin, the 90% Log transformed confidence intervals for both C_{max} and AUC were outside the acceptable range of 80-125%. [Hercon versus Transderm-Nitro: LN(Cmax), 106% -152% and LN(AUC0-24), 97%-130%, Hercon versus Key: LN(C_{max}), 106%-152% and LN(AUC0-24), 101%-137%.] The AUC values for 1,2-dinitroglycerin, Hercon versus Key, were also outside the acceptable range of 80-125%."

Response 1 a:
Provided in support of this amendment is a new bioequivalence study conducted on a reduced-size Hercon patch. The results yielded confidence intervals for Hercon vs. Transderm-Nitro® that were all within the 80-125% range for intact nitroglycerin and the primary 1,2-dinitroglycerin metabolite. The study conclusion is that the re-sized Hercon product and Transderm-Nitro® are bioequivalent.

Deficiency 1 b:
"There is a discrepancy in the number of data set reported in the mean data and the data used in the statistical analysis (ANOVA). In the future submission, you are advised to report the results only from subjects who completed both test and reference products."

Response 1 b:
In the new study provided in support of this amendment, the statistical analysis was conducted only for the 36 subjects who completed both treatments.

Deficiency 1 c:
"The data reported in the mean data calculation and in the variance analysis (ANOVA) are inconsistent. In the mean data calculation, those samples with assayed values less

than the limit of quantitation (LOQ) were apparently treated as "missing" (see the count, N, in the mean data). During the procedure of ANOVA, those samples with assayed values less than LOQ were reported as "zero". In the future submission, you are advised to be consistent in the data presentation and to report those values less than LOQ as zero."

Response 1 c:
The data presentation in the new study is consistent, and those samples with assayed values below the limit of quantitation are reported as, "zero."

Deficiency 1 d:
"You described how the time to steady state was determined. Criterion 1 (requires no significant differences among the concentrations observed at each time point prior to the steady state time) appears to be in error. Please describe how this would affect the values of C_{max}, C_{min}, C_{av}, and the value of degree of fluctuation (DF). Since this information is not considered to be the primary parameters for bioequivalence, at the present time the error in the determination of time to steady state is considered, not to affect the conclusion of the study."

Response 1 d:
The new study does not include calculation of "time to steady state" because, as noted, this information is not considered to be one of the primary parameters for assessing bioequivalence. The power of the new study was sufficient to result in a determination of bioequivalence based on the AUC and C_{max} pharmacokinetic parameters.

Deficiency 1 e:
"The batch size of the test product was not reported."

Response 1 e:
The batch size was available elsewhere in the ANDA (executed batch record and stability sections), but due to an oversight was not listed in the Bioequivalence Sections. The theoretical batch size was patches. Note that the actual patch yield was somewhat less, at units, because for a coating process on the large-scale production equipment, set-up losses are a much larger percentage of units for a smaller batch size.

For the batch manufactured for the new biostudy in support of this amendment, the batch size is stated in the Bioequivalence (In Vivo Study) Section, as well as in the Executed Batch Record and Stability Sections.

Deficiency 1 f:
"The residual content of nitroglycerin in the used patches was determined but not submitted."

Response 1 f:
Hercon regrets this oversight. For the new study, a complete report describing the testing of returned patches is provided in the Bioequivalence (In Vivo Study) Section, VI.B.

Deficiency 1 g:
"It should be noted that each test patch was applied for 24 hours, which is different from the dosing schedule (i.e., to include a daily patch-off period of 10-12 hours) specified in the labeling of this drug product. In the future submission you are advised to apply the patch for 12-14 hours. Please be advised that an IND may be required for outside-labeling use."

Response 1 g:
For the bioequivalence study submitted in April 1993 in support of this application, Hercon had received no written response from the Division of Bioequivalence even after one year had elapsed. Based upon verbal comments we had received, it was clear that the Division would require at least some additional evidence of bioequivalence, if not a new study on a reformulated product. Since so much time had elapsed, Hercon decided to evaluate re-sizing of the product, since the amount of nitroglycerin delivered from a patch is known to be linearly related to the area of the applied system. From the results of the previous study on 15.0 cm^2 product, Hercon calculated that a 10% reduction in size (to 13.5 cm^2) should result in a product which meets the guideline confidence intervals for concluding bioequivalence for nitroglycerin and its principal metabolites, 1,2-glyceryl dinitrate and 1,3-glyceryl dinitrate.

With this information, and before receiving a response from the Agency, Hercon ventured to initiate another bioequivalence study using the smaller-sized 13.5 cm^2 product. The study design was similar to that of the previous study; that is, the patch was worn for 24 hours. In this new study, however, the area under the curve (AUC) was evaluated at 14 hours as well. This was done not only to comply with the current labeling, which recommends a 12-14 hour patch-on period followed by a 10-12 hour patch-off period, but also to comply with the former approved labeling that called for the patch to be worn continuously for 24 hours. There is no safety concern in healthy normal subjects, as nitroglycerin patches were safely and successfully utilized for many years with a 24 hour administration period. Further, these dosing periods are merely recommendations, as the appropriate minimum nitrate-free interval, if any, has not yet been fully defined.

In many of the countries outside the U.S., physicians continue to prescribe the product for 24 hour wear. Thus, it could be useful for an evaluation of bioequivalence to include both a 14 hour and a 24 hour administration so that there is evidence to show the products are the same in either case. Furthermore, since many countries require bioequivalence evaluation for nitroglycerin patches to be based on 24 hour wear, this approach avoids the unnecessary clinical research brought about by doing two studies– one for 14 hour wear and one for 24 hour wear– to gain approval in the U.S. and abroad. This is particularly relevant for studies assessing bioequivalence with Transderm-Nitro®, which is more commonly regarded as the transdermal nitroglycerin reference product outside the U.S.

Again, this new study was initiated prior to our having received the Division's comment stating that the patch should be worn for only 14 hours. It should be noted that the patch dosage ("one patch per day") is the same as currently approved, and the total daily dose employed in the study (0.4 mg/hr x 24 hr = 9.6 mg) is less than the total daily dose obtained by 14 hour wear of the largest conditionally-approved patch strength (0.8 mg/hr x 14 hr = 11.2 mg), thus is not subject to the IND requirements under 21 CFR § 320.31(b)(1).

Deficiency 1 h:
"The drug release data were derived from 6 dosage units. You are advised that in vitro dissolution (drug release) testing should be conducted on 12 individual units of the test and reference products and the summary report should include the raw, mean, range, and coefficient of variation data."

Response 1 h:
For the new study, drug release data were derived from 12 individual units, with samples taken to match each blood sampling time from the biostudy. A complete report, which includes raw data, mean, range, and RSD, is provided in the Bioequivalence (In Vitro Dissolution) Section, VI.D.

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2. WEAR AND REPEATED INSULT PATCH TEST

Deficiency 2 a:
"Eighty-six (86) subjects completed the induction phase of the study. According to the study protocol, each subject received 24-hour patch applications three times a week (on Monday, Wednesday, and Friday) for three weeks and for each patch application the sites were scored at 24-hour and 48-hour. The irritation scores at 24-hour and 48-hour showed a total number of eighty six. Please clarify whether the scores reported were

mean values. If those were mean values then you should report the mean, range, and coefficient of variation of the data as well."

Response 2 a:
We presume that the irritation scores to which you refer are those shown on pages 2/53 and 3/53 of the report (and repeated on page 1 of Appendix B of that same report). As correctly noted in both places in the report, the scores reported are "peak" scores and not averages. Evaluation of the peak (or highest) irritation score seen during the induction phase was done to avoid diluting any potential irritancy effect seen. Since the scores are not averages, then, descriptive statistics were not provided.

Deficiency 2 b:
"There is a discrepancy in the number of data set (i.e., N) reported in the challenged phase. You should clarify why N for the 48-hour score is more than that of the 24-hour score."

Response 2 b:
The "discrepancy" occurred because two subjects did not report for the 24 hour evaluation, but both did return for the 48 hour evaluation. These events were documented on pages 40/53 and 49/53 of the report:

Subject #111 (treatments A&B) missed the 24 hour evaluation
Subject #116 (treatments C&B) missed the 24 hour evaluation

Similar occurrences are noted for the wear scores on page 46/53. As seen on pages 43/53 and 52/53, however, those subjects (#111 and #116) did report for the 48 hour site evaluation, and their scores were entered into the evaluation.

Note that whether these subjects' 48 hour scores are included or excluded, the study results are the same.

Deficiency 2 c:
"The bioequivalence study on 0.4 mg/hr patch was conducted while the wear and repeated insult patch study was conducted on 0.2 mg/hr patch. The observation made on the wear properties and the irritation potential of this study pertains only to the 0.2 mg/hr patch and the study does not establish that the larger patches have acceptable skin irritation characteristics."

Response 2 c:
Because of the likelihood of severe headaches with higher doses of nitroglycerin, this study was conducted on the smaller patch size of the product to minimize potential dropouts due to intolerance to headache. The 7.5 cm^2 patch size was used in the study,

but the per-area formulation of the re-sized product is the same. Thus, the results still support the new, slightly smaller product size.

It should be noted that as part of the protocol for the new bioequivalence study on the larger 0.4 mg/hr product strength, clinical evaluations were made of the relative irritation and residual adhesive observed after administration of the two treatments. The clinical observations showed no significant difference in skin irritation between the two products, and the Hercon product left less residual adhesive on the skin upon removal.

Hercon Laboratories trusts that these responses, and the complete amendment provided herewith, will be sufficient to remove the cited deficiencies and allow completion of the Agency's review of our application. If you have any questions or need any additional information, please do not hesitate to contact the undersigned at your convenience.

We hereby certify that a complete copy of this amendment has been sent concurrently to Hercon's home FDA District Office (Philadelphia District).

Very truly yours,

Joseph J. Sobecki, R.A.C.
Senior Director
Regulatory Affairs
Hercon Laboratories Corporation

JJS:js
attachments

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MAJOR AMENDMENT

April 29, 1994

NDA ORIG AMENDMENT
N/AC
Draft

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

via Federal Express
airbill # 085597046

RECEIVED
MAY 0 3 1994
GENERIC DRUGS

RE: **ANDA 89-884**; Nitroglycerin Transdermal System, 0.2 mg/hr
ANDA 89-885; Nitroglycerin Transdermal System, 0.4 mg/hr
ANDA 89-886; Nitroglycerin Transdermal System, 0.6 mg/hr

Dear Sir or Madam:

Reference is made to Dr. Greg Guyer's October 29, 1993 not approvable letter concerning the Abbreviated New Drug Applications identified above. To address the deficiencies cited therein, Hercon is providing this Amendment to our applications. As noted in Dr. Guyer's letter, this amendment is to be considered a Major Amendment.

The numbering system of the responses set forth below corresponds with that of the deficiencies cited in Dr. Guyer's October 29, 1993 letter. All of the requisite documentation to respond to each individual deficiency is generally grouped together under a single attachment Tab as described in the written response for that deficiency.

A.
1

Received 5/9/94

2. Regarding other ingredients:

a. A copy of the DMF authorization letter ( ) provided to FDA for DMF ( ) covering acrylic polymers ( ) is included under **Tab 4.**

b. A revised cover page for the "Inactive Ingredients" section, which identifies acrylic polymers ( ) and references ( ) DMF for the relevant composition and control information, is provided under **Tab 5.**

c. Copies of the supplier's COAs for the silicone treated release liner , raw material numbers 418-86 and 4199-92 are provided under **Tab 6.** A discussion of testing performed by release liner suppliers, which is germane to these materials as well, is presented under 4.c. below.

3. Regarding manufacturing and processing:

Redacted 2

pages of trade

secret and/or

confidential

commercial

information

4. Regarding container/closure:

a. A report describing the results of our testing to determine the level at which nitroglycerin is seen in the liner is included under **Tab 11**. In summary, while the nitroglycerin level in the liner seems to increase slightly with time, the level is very small, even after 18 months, and is of no practical significance to the shelf-life of the product.

b. Provided under **Tab 12** is a report describing performance of the USP <671> water vapor transmission testing as well as an instrumental water vapor transmission test on the packaging film itself. The results demonstrate minimal to no water vapor transmission.

c. The document presented on page 1581 is representative of the material certification received from the supplier. The manufacturer typically reports results from the "release" test, which is not critical to Hercon's use of the material but which many of our supplier's other customers require for their applications of the material. Upon receipt of the material, Hercon performs film weight and thickness testing to assure the correctness of the base stock of the liner. Additionally, Hercon performs an identity test by IR spectrum to assure the presence of the silicone treatment.

d. Physicochemical tests for the 302 and 304 Packaging Films per USP XXII/NF XVII <661>, while not strictly relevant due to the multilayered structure of the films, have been performed at your request. The results are provided under **Tab 13**.

e. Rather than the vacuum leak test, which is more commonly employed for oral dosage forms packaged in a blister configuration, Hercon employs the burst test to measure the sealing quality of the finished packages. A copy of the test method is provided under **Tab 14**. Also included are results of testing performed for six product lots previously manufactured for stability testing. Hercon intends to employ this method during the validation process to assure that the validated sealing parameters provide adequately sealed dosage units.

5. Regarding laboratory controls:

Redacted 1

pages of trade secret and/or confidential commercial information

6. Regarding the adhesive:

a. We would expect adequate adhesion to be maintained even under conditions of perspiration and bathing, as the adhesive is not water-based. The adhesive wear properties/RIPT study included in our application (beginning on page 1160) involved a number of 24-hour administrations of the product under conditions of normal daily activity, including showering and bathing. The results demonstrated very good adhesion, with relatively few patches dislodging.

An additional wear properties study was recently conducted, as described under b. below. In that study the subjects were specifically requested to keep a diary of any showering, bathing, or swimming, and to indicate whether any patch loosening or dislodging occurred after those activities. During the study, most of the subjects either showered or bathed while wearing each test product. Although a few of the Hercon patches which fell off were identified as having done so at the time of showering or bathing, the number of dislodged patches was very small, and over 90% of the Hercon patches on subjects who showered or bathed remained adequately adhered. Overall, the adhesion quality of the Hercon patch was acceptable, and comparable to that of a marketed reference patch.

b. In response to this query, we have conducted a wearability/irritation study using aged product that was approximately 18 months old, a freshly-manufactured lot of product, and a marketed reference product. The batch of aged Hercon product was the same lot tested in the original Wear Properties/RIPT study noted above, which begins on ANDA page 1160, and thus provides an excellent point of reference. A complete report of this study is provided under **Tab 19**.

The results demonstrated that although the adhesion for the aged product was slightly lower than that of the reference product or the freshly-manufactured lot, the results were not statistically significant. Further, the adhesion of the aged lot was still acceptable, with a mean quality of wear score of 4.21 on a scale of 0 to 5 (with 5 being full adhesion, and 4 meaning approximately 1/4 of the adhesive area loose). In the original study, the same batch resulted in a mean adhesion quality (on the same scale) of 4.25, a virtually identical result. It can thus be concluded that the adhesion quality of the aged product is comparable to that of freshly-manufactured product as well as to a marketed reference product.

7. Regarding method validation:

8. Regarding stability:

a. The sampling recommendation in the guideline for two containers at each station, in context, appears to relate to multiple-dose containers such as tablet bottles. It is targeted at assuring that a sufficient number of previously-unopened containers is sampled at each stability station. Hercon's Nitroglycerin Transdermal System is a unit dose product; thus, every patch used is in a previously-unopened container. On this basis, we sample over a dozen individual containers at each stability station.

The product units sampled for stability are randomly taken from throughout the finished lot and are thus representative of the batch as a whole, as required by the guideline. In general, the desired quantity of stability samples is compared with the total number of

shelf cartons and/or shipper cases available to determine the quantity of samples to remove from the various shippers to assure a representative sample. For the "bio batch", for which the executed batch record is provided in the application, 26 samples were removed from each of 31 available shipping cartons to yield approximately the desired 800 samples (actually 806). Documentation of this sampling is shown in the batch record on ANDA page 1530.

b. The Total Degradation Products test has been added to the stability program, as stated under 5.g. and 7.b. above. Provided under **Tab 24** are updated stability data summaries which include the results of Degradation Products testing at approximately the 18 month interval. Future stability test stations for those lots will include the Degradation Products test.

c.i. As stated in step

B. Labeling Deficiencies

General Comments:

1. We note that the cartons and pouches for the three strengths, which were presented approximately actual size, are significantly different in size. However, to more prominently differentiate the three strengths, we have dramatically enlarged and increased the prominence of the strength indication on the pouches and cartons.

2. We did indeed include at least four copies of draft labeling as required. Unfortunately, neither the regulation cited nor any written guidance identifies where those four copies are to be placed among the various sections and volumes required to be submitted. We have contacted the Office of Generic Drugs for appropriate guidance for future submissions. In this submission, four copies of draft labeling are provided - one in the archival copy and three in the review copy.

Foil Pouch:

Hercon does normally include an identifying specification number and a revision date on all labeling, but unfortunately these were inadvertently omitted on the draft copy. The revised draft pouch label under **Tab 26** includes these identifying marks; but please note

that their actual final location will be determined by space available upon typesetting of the final printed labeling.

Carton:

1. The word, "a" has been deleted from the Federal caution statement.

2. Again, Hercon does normally include an identifying specification number and a revision date on all labeling, but unfortunately these were inadvertently omitted on the draft copy. The revised draft carton labeling under **Tab 27** includes these identifying marks; but please note that their actual final location will be determined by space available upon typesetting of the final printed labeling.

Patient Package Insert:

A revised draft patient insert is provided under **Tab 28**. The insert is in accord with that for Transderm-Nitro® (6/89), except for those changes necessary due to the differences between the two products.

Insert:

Draft copy of the revised insert is included under **Tab 29**. As requested, the following changes have been made:

DESCRIPTION:

Although the regulations do not require inclusion of this information, we have added a listing of inactive ingredients. For this type of product, this listing is unfortunately of minimal use to the public because of the generality made necessary by the highly trade-secret nature of the specific composition of the backing film and adhesive.

INDICATIONS AND USAGE:

This section has been revised as requested.

ADVERSE REACTIONS:

1. The word, "**OVERDOSAGE**" has been made bold, capitalized.

2. The additional paragraph you identified has been added.

OVERDOSAGE:

The hyphen has been replaced by, "to".

DOSAGE AND ADMINISTRATION:

The words, "**CLINICAL PHARMACOLOGY**" have been made bold, capitalized.

We note that the referenced samples for methods validation were collected by an FDA representative on November 22, 1993. Based upon a question from Nicholas Falcone of the FDA Philadelphia District Lab, we have revised the product Dissolution test method to more clearly identify the reference to the USP dissolution apparatus. A copy of the revised method is included under **Tab 30.**

We note further that although your letter states that we will be notified in a separate letter of any deficiencies in the bioequivalence portion of our application, we have not yet had any response from the Division of Bioequivalence, although the review is now pending one full year.

Hercon Laboratories trusts that these responses will be sufficient to remove the cited deficiencies and allow completion of the Agency's review of our application. If you have any questions or need any additional information, please do not hesitate to contact the undersigned at your convenience.

We hereby certify that a complete copy of this amendment has been sent concurrently to Hercon's home FDA District Office (Philadelphia District).

Very truly yours,

Joseph J. Sobecki, R.A.C.
Senior Director
Regulatory Affairs
Hercon Laboratories Corporation

JJS:js
attachments

HERCON
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AILABILITY

MAJOR AMENDMENT

April 27, 1993

NDA ORIG AMENDMENT

RECEIVED

APR 2 8 1993

GENERIC DRUGS

Roger L. Williams, M.D., Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

RE: **ANDA 89-886**; Nitroglycerin Transdermal System, 0.6 mg/hr

Dear Dr. Williams:

Enclosed please find an amendment to the subject ANDA identified above. We have reformulated the product that is the subject of this application, and performed the necessary bioavailability testing. The formulation, methods, and controls differ substantially from those for the previous formulation. Further, a significant period of time has elapsed since the original filing. During that time, the "state of the art" of ANDAs has been greatly refined, and the Agency has provided significant guidance to industry as to the format and content of ANDA submissions. In order to provide for the reformulation, comply with the Office's Policy and Procedure Guide #30-91, and simplify the review process, this amendment has been designed as a complete application in and of itself. Thus, all materials previously submitted to this application are hereby moot and should be considered replaced by this amendment. Accordingly, please disregard all previously submitted information. We hope this will greatly facilitate review of our application.

As mentioned, the format of this submission corresponds with that suggested in Policy and Procedure Guide #30-91. The archival copy consists of three separate volumes. Volume 1 of 3 contains sections I.-VI.A. and part of section VI.B. Volume 2 of 3 contains the remainder of section VI.B. and sections VI.C.-VI.E. Volume 3 of 3 contains sections VII.-XX. The chemistry review copy (red) contains sections I.-V. and VII.-XX., an additional copy of labeling in section V., and two separately bound copies of the methods validation package (sections XVI.A. and XVI.B.). The bioavailability review copy (orange) consists of two volumes. The first contains sections I.-VI.A. and part of VI.B., while the second contains the remainder of section VI.B.-VII.

The pages are numbered sequentially in the **upper right-hand corner**. Some documents contained in the application, most notably the bioequivalence report, were numbered on the bottom by the contract research organization (C.R.O.) using a similar numbering machine. In these cases, the C.R.O.'s number has been crossed out with a single line as a reminder. Only the numbers in the upper right-hand corner are relevant to the indexing of this application.

Waiver 5-4-93

If you have any questions about this submission, please do not hesitate to contact me. We look forward to your favorable review.

Very truly yours,

HERCON LABORATORIES CORPORATION

Joseph J. Sobecki, R.A.C.
Director of Regulatory Affairs

HERCON
LABORATORIES CORPORATION

P.O. Box 786, York, PA 17405 Phone: (717) 764-1191 Fax: (717) 764-5395 Telex: 401571

2.1

NA 8/19/92

NEW CORRESP

August 20, 1992

RECEIVED
AUG 24 1992
GENERIC DRUGS

Roger L. Williams, M.D.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
5600 Fishers Lane
Rockville, Maryland 20857

Re: [redacted] Nitroglycerin Transdermal System, 0.6 mg/hr
(formerly 15 mg/24 hrs)

Dear Dr. Williams:

As requested in an August 19, 1992 telephone call from Ms. Valerie Vashio of your office, this is to confirm our intent to pursue approval of this application.

Hercon is in the process of preparing an amendment to be submitted before the end of this year, which will make moot all cited deficiencies.

If you have any questions, please do not hesitate to contact me at your convenience.

Very truly yours,

HERCON LABORATORIES CORPORATION

Joseph J. Sobecki
Director of Regulatory Affairs

JJS/cls

cim
9-1-92

Hercon Laboratories Corporation
A Subsidiary of
HEALTH-CHEM CORPORATION

P.O. Box 786
York, PA 17405
(717) 764-1191 TELEX: 401571 TELEFAX: (717) 764-5395

June 1, 1989

Carl C. Peck, M.D., Director
Center for Drug Evaluation and Research
Attention: Document Control Room
Division of Generic Drugs
Food and Drug Administration
HFD-232, Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

ORIG NEW CORRES

RE: ANDA 89-886
Nitroglycerin Transdermal System, 0.6 mg/hr (15 mg/24 hours)

Dear Dr. Peck:

Reference is made to the above pending Abbreviated New Drug Application. This is to advise you that the address to which correspondence should be sent, and the responsible official or agent who is to receive such correspondence concerning this Application, have changed.

Effective immediately, all correspondence concerning this or any other Hercon Application should be sent to:

Hercon Laboratories Corporation
Subsidiary of Health-Chem Corporation
P.O. Box 786
York, PA 17405
Attention: Joseph J. Sobecki
Manager, Regulatory Affairs

Enclosed is a signed copy of FDA Form 356-h, which contains these revisions. The manufacturing facility and all other commitments remain the same as specified in our Application.

We would like to take this opportunity to again confirm that we are in the process of compiling information to repond to Dr. Seife's letters of February 17, April 25, and August 31, 1988. Appropriate responses will be submitted as soon as possible.

If you have any questions, or require any clarification regarding this address change, please do not hesitate to contact the undersigned at 717-764-1191 at your convenience.

Sincerely,

HERCON LABORATORIES CORPORATION

Joseph J. Sobecki
Manager, Regulatory Affairs

RECEIVED
JUN 6 1989
GENERIC DRUGS

Enclosure
Desk Copy: Mr. David Rosen; HFD-232, Room 17B-25

Hercon Laboratories Corporation
A Subsidiary of
HEALTH-CHEM CORPORATION
Research & Development Laboratories
2008 Corporate Court, Middlesex Business Center, So. Plainfield, N.J. 07080
(201) 755-7730 Telex: 4973834 HERC UI Facsimile: (201) 755-7278

Orig

May 11, 1988

Dr. Marvin Seife
Director
Division of Generic Drugs
Office of Drug Standards
Center of Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA ORIG AMENDMENT

DRAFT LABELING

Subject: Your Letter Dated April 25, 1988
Transdermal Nitroglycerin System, 15 mg/24 hrs
ANDA # 89-886

Dear Dr. Seife:

Enclosed is the revised draft labeling for the subject product per your comments of April 25th. This labeling includes:

- direct patch labeling
- backing labeling
- carton labeling
- patient package insert
- professional insert

As requested in your February 17th letter, enclosed is a copy of the new) DMF referral letter dated March 14, 1988. Your other comments are being addressed and a response will be forwarded upon availability.

If you have any questions or comments, please contact me.

Sincerely,

Janine Laurencot

Janine Laurencot
Manager, Government Regulations

JL:plp

Enclosures

RECEIVED
MAY 12 1988
GENERIC DRUGS

Hercon Laboratories Corporation
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HEALTH-CHEM CORPORATION

Research & Development Laboratories
2008 Corporate Court, Middlesex Business Center, So. Plainfield, N.J. 07080
(201) 755-7730 Telex: 4973934.HERC UI Facsimile: (201) 755-7278

March 11, 1988

Dr. Marvin Seife
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drug Evaluation
and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Subject: Your letter of February 17, 1988.
Nitroglycerin Transdermal System,
15 mg/24 hrs (ANDA # 89-886)

Dear Dr. Seife:

Enclosed please find the revised proposed labeling for ANDA # 89-886. This labeling includes:

- direct patch labeling
- backing labeling
- carton labeling
- patient package insert
- professional insert

The trade name of the product has been changed to Transdermal Nitroglycerin System, 15 mg/24 hrs. Since Hercon is proposing three nitroglycerin products, identical in all respects except for size - ($10cm^2$, 20 cm^2, 30 cm^2), we need to include the delivery rate in the product name.

Your other comments are being addressed and I will forward a response as the information becomes available. If you have any questions or comments, please contact me.

Sincerely,

Janine Laurencot

Janine Laurencot
Manager of Government Regulations

JL/kph

RECEIVED
MAR 17 1988
GENERIC DRUGS

Hercon Laboratories Corporation
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HEALTH-CHEM CORPORATION

Research & Development Laboratories
2008 Corporate Court, Middlesex Business Center, So. Plainfield, N.J. 07080
(201) 755-7730 Telex: 4973934 HERC UI Facsimile: (201) 755-7276

Drug

March 10, 1988

ORIG NDA COPIES!

Dr. Marvin Seife
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Subject: ANDA-89-886; Nitroglycerin Transdermal System,
15 mg/24 hrs. Your letter of February 17, 1988

Dear Dr. Seife:

In response to your concern regarding the skin irritation study submitted on November 12, 1988, enclosed is a copy of page 3 of the study (144 a + b). Please note that it was concluded that the sample did not induce primary irritation or allergic contact dermititis in human subjects.

If you have any additional questions or comments, please contact me.

Sincerely,

Janine Laurencot

Janine Laurencot
Manager of Government Regulations

JL/kph

Enclosure

RECEIVED
MAR 17 1988
GENERIC DRUGS

Hercon Laboratories Corporation
A Subsidiary of
HEALTH-CHEM CORPORATION
Research & Development Laboratories
200B Corporate Court, Middlesex Business Center, So. Plainfield, N.J. 07080
(201) 755-7730 Telex: 4973934 HERC UI Facsimile: (201) 755-7276

Drug

89-986

December 4, 1987

Dr. Marvin Seife
Director, Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics
HFN-230, Room 16-72
5600 Fishers Lane
Rockville, MD 20857

ONE [illegible]

Attn: Mr. David Rosen

Subject: Hercon Nitroglycerin Transdermal System releasing 15 mg/24 hrs.

Enclosed are copies of a revised Form 356H for the Abbreviated New Drug Application for the subject product. Please note the reference product for this submission is controlled release nitroglycerin ointment (Nitro-Bid^{R}, from Marion Laboratories). The subject product complies with the requirements of the Federal Register Notice for such products, dated September 15, 1978, Vol. 43, No. 180.

Additionally, the subject product is substantially identical to previously approved (ANDA 88-783) transdermal nitroglycerin product, NTS-15 (Nitroglycerin Transdermal System) from Bolar Pharmaceutical Company, Inc. The only change between the approved product and the subject product is the subject product employs a different adhesive and backing for the adhesive to secure the patch to the skin. The other components used in the subject product have been previously reviewed and found acceptable.

Also enclosed is a revised Comparison with the Listed Product, and Section 505(j)(2)(A) information.

We look forward to a prompt review of this Application. If there are any questions or comments, please contact us.

Sincerely yours,

Laura Zeoli

Laura T. Zeoli
Vice President
Corporate Development

Janine Laurencot

Janine Laurencot
Manager of
Government Regulations

RECEIVED
DEC 7 1987
GENERIC DRUGS

/rt

Encl.

Hercon Laboratories Corporation
A Subsidiary of
HEALTH-CHEM CORPORATION
Research & Development Laboratories
2008 Corporate Court, Middlesex Business Center, So. Plainfield, N.J. 07080
(201) 755-7730 Telex: 4973934 HERC UI

Firm must cite FR notice as listed and certify on drug and its labeling to comply to FR notice and cite the Federal product as patterned
RPolli
12/3/87

November 12, 1987

Dr. Marvin Seife
Director, Division of Generic Drugs
Office of Drugs Standards
Center for Drugs and Biologics
HFN-230 Room 17B-45
5600 Fishers Lane
Rockville, MD 20857

DO NOT Send Dup TO Bio

RE: Nitroglycerin Transdermal System
Releasing 15mg/24 hours

Dear Dr. Seife:

Enclosed is an Abbreviated New Drug Application, submitted pursuant to Section 505 of the Federal Food Drug and Cosmetic Act, for the above mentioned product.

The submission contains an ARCHIVE COPY of all technical sections, and separately bound volumes of the individual technical sections, to serve as REVIEW COPIES. Draft labeling for the drug product and a Method Validation Package, in triplicate, to be used by your testing laboratory upon request of samples, are included in this submission.

The Nitroglycerin Transdermal System releasing 15mg/day is identical to Hercon's current product NTS-15 in every respect except for the backing material. The NTS-15 product incorporates a foam backing whereas the subject of this application incorporates a vinyl backing. The type of backing (i.e foam or vinyl) serves only as a vehicle of application for the unit dosage form to the patient's skin. The presence of a heat seal barrier film to the cover film and along the perimeter of the drug reservoir separates the backing of the product and the drug reservoir. The backing is not affected by the components of the drug product. Since the drug reservoirs are identical in both products, the release rate of nitroglycerin is also identical.

If there are any questions on the enclosed, please contact me or Laura Zeoli.

Sincerely,

AGIS F. KYBONIEUS, Ph.D.
President

AFK/kd
Enclosures

RECEIVED
NOV 16 1987
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